510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number: K040133

B. Purpose for Submission:

Premaket Notification 510(k) of intention to manufacture and market a new device, Dimension® Urine Amphetamine/Methamphetamine Screen Flex® reagent cartridge (DF91B)

C. Analyte: Amphetamine

D. Type of Test:

Qualitative or Semi-Quantitative homogeneous enzyme immunoassay

E. Applicant: Dade Behring Inc.

F. Proprietary and Established Names:

Dimension® Urine Amphetamine/Methamphetamine Screen Flex® reagent cartridge

G. Regulatory Information:

1. Regulation section: 21CFR §862.3100 Amphetamine test system
2. Classification: Class II
3. Product Code: DKZ
4. Panel: Toxicology (91)

H. Intended Use:

1. Intended use(s):

The AMPH Flex® reagent cartridge used on the Dimension® clinical chemistry system provides reagents for an in vitro diagnostic test intended for the qualitative and semi-quantitative determination of amphetamines in human urine using a cutoff of either 300, 500, or 1000 ng/mL. Measurements obtained with the AMPH method are used in the diagnosis and treatment of amphetamines use or overdose.

2. Indication(s) for use:

Measurements obtained with the AMPH method are used in the diagnosis and treatment of amphetamines use or overdose.

3. Special condition for use statement(s):

The AMPH method provides only a preliminary analytical test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. Gas chromatography/mass spectrometry (GCMS) is the preferred confirmatory method. Other chemical confirmation methods are available. Clinical consideration and professional judgement should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

4. Special instrument Requirements:

To be used on Dade Behring Dimension® clinical chemistry systems for the qualitative and semi-quantitative determination of amphetamines in human urine.

I. Device Description:

The Dade Behring Dimension® AMPH method is an in vitro diagnostic device that consists of prepackaged reagents in a plastic cartridge (Flex®) for use on the Dade Behring Dimension® clinical chemistry system**.**

Wells[a]	Form	Ingredient	Concentration	Source
1	Empty			
2,3	Liquid	d-amphetamine and d-methamphetamine enzyme conjugates[b] , bovine serum albumin	B	
4	Empty			
5,6	Liquid	Monoclonal antibodies[b] reactive to d-amphetamine and d-methamphetamine, bovine serum albumin, NAD+, G6P	B	mouse
7	Empty			
8	Liquid	Monoclonal antibodies[b] reactive to d-amphetamine and d-methamphetamine, bovine serum albumin, NAD+, G6P	B	mouse

J. Substantial Equivalence Information:

1. Predicate device name(s): Syva® Emit II Plus Amphetamine Assay

2. Predicate K number(s): k031004

3. Comparison with predicate:

This product is substantially equivalent to other enzyme Immunoassay Amphetamine assays, such as the Syva® Emit II Plus Amphetamine Assay (k031004) for the 30-R Biochemical System

Similarities		
Item	**Device**	**Predicate**
	Dade Behring Inc. Amphetamine/Methamphetamine Assay (K040133)	Syva® Emit II Plus Amphetamine Assay for the 30-R Biochemical System (K031004)
Intended Use	in–vitro use, qualitative and semi-quantitative analysis of amphetamines	in–vitro use, qualitative and semi-quantitative analysis of amphetamines
Sample Type	Human Urine	Human Urine
Cutoffs	300, 500, or 1000 ng/mL	300, 500, or 1000 ng/mL
Technology	Homogeneous Enzyme Immunoassay Emit® Technology	Homogeneous Enzyme Immunoassay Emit® Technology
Main Ingredients	Monoclonal antibodies reactive to d-amphetamine and d-methamphetamine NAD+, G6P	Monoclonal antibodies reactive to d-amphetamine and d-methamphetamine NAD+, G6P

K. Standard/Guidance Document Referenced (if applicable):

Reproducibility testing was done in accordance with the NCCLS Approved Guideline for User Evaluation of Precision Performance of Clinical Chemistry Devices EP5-A, 1999**.**

L. Test Principle:

The Dade Behring Dimension® clinical chemistry system Flex® Reagent Cartridge Urine/Amphetamine/Methamphetamine Screen Flex® reagent cartridge assay is a homogeneous enzyme immunoassay technique used for the analysis of specific compounds in human urine. The assay is based on competition between drug in the specimen and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for antibody binding sites. Enzyme activity decreases upon binding to the

antibody, so the drug concentration in the specimen can be measured in terms of enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that is measured spectrophotometrically. Endogenous serum G6PDH does not interfere because the coenzyme NAD functions only with the bacterial (Leuconostoc mesenteroides) enzyme employed in the assay. The reaction sequence is shown below:

Ab+AMPH + AMPH - G6PDH → Ab – AMPH + Ab – AMPH – G6PDH (inhibited) + AMPH-G6PDH (active)

Glucose-6-Phosphate + NAD+ + AMPH-G6PDH (active) → 6-phosphogluconolactone + NADH + H (absorbs at 340nm)

Where:
Ab= antibody reactive to d-amphetamine and d-methamphetamine
AMPH = amphetamines and methamphetamine
AMPH- G6PDH = d-amphetamine and d-methamphetamine glucose-6-dehydrogenase conjugates**.**

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Syva Emit® Cutoff Calibrators (levels 300, 500, and 1000 ng/mL) and in-house controls (levels 225, 375, 625, 750 and 1250 ng/mL) prepared at Date Behring were analyzed in duplicate for 20 days. The within-run and total coefficients of variation (%CV) were calculated by the analysis of variance method according to the National Committee of Clinical Laboratory Standards (NCCLS) Guideline EP5-A (February 1999).

Calibrator/Control[d]	Reproducibility at 300 and 500 ng/mL cutoffs				
		Within		Total	
	Mean	SD	CV	SD	CV
ng/mL	ng/mL	ng/mL	%	ng/mL	%
225	228	11.2	4.9	23.3	10.2
300	290	11.2	3.9	23.2	8.0
375	375	9.6	2.6	26.8	7.1
500	499	35.4	7.1	38.7	7.9
625	661	38.4	5.8	55.3	8.4

Calibrator/Control[d]	Reproducibility at1000 ng/mL cutoffs				
		Within		Total	
	Mean	SD	CV	SD	CV
ng/mL	ng/mL	ng/mL	%	ng/mL	%
750	766	24.1	3.1	36.2	4.7
1000	1006	20.0	2.0	28.5	2.8
1250	1285	44.3	3.4	60.0	4.7

[d] = Syva® Emit® calibrators and in house controls

b. Linearity/assay reportable range:

Samples were prepared by spiking known amounts of methamphetamine and amphetamine into a negative urine pool. Mean results in the qualitative and semi-quantitative modes were calculated from 5 replicates of each spikes level.

Mean results of methamphetamine and amphetamine spikes, were correctly qualified as negative or positive relative to each of the three cutoffs in the semi-quantitative mode.

Qualitative Recovery

SampleVolume:	**3µL**	**6 µL**	
	Qualitative Result Relative to 1000 cutoff (+/-)	**Qualitative Result Relative to 300 cutoff (+/-)**	**Qualitative Result Relative to 500 cutoff (+/-)**
Cutoff Rate (mau/min)	216.0	183.3	210.8
Meth (ng/mL)			
150		-	-
200	-	-	-
350	-	+	-
450	-	+	-
600	-	+	+
750	-	+	+
900	-	+	+
1300	+	+	+
1500	+	+	+
1800	+	+	+
Amph (ng/mL)			
150		-	-
200	-	-	-
350	-	+	-
450	-	+	-
600	-	+	+
750	-	+	+
900	-	+	+
1300	+	+	+
1500	+	+	+
1800	+	+	+

Semiquantitative Recovery

Nominal	3 µL/ 1000 ng/mL Meth Mean Conc. Of Spiked Sample		6 µL/ 1000 ng/mL Meth Mean Conc. Of Spiked Sample	
(ng/mL)	ng/mL	%	ng/mL	%
Meth				
150			*135*	*90%*
200	*238*	*119%*	*201*	*100%*
350	*393*	*112%*	*354*	*101%*
450	*490*	*109%*	*478*	*106%*
600	*629*	*105%*	*591*	*98%*
750	*777*	*104%*	*812*	*108%*
900	*901*	*100%*	*902*	*100%*
1300	*1384*	*106%*		
1500	*1510*	*101%*		
1800	*1958*	*109%*		
Amph				
150			202	135%
200	173	86%	217	108%
350	406	116%	319	91%
450	457	102%	467	104%
600	591	98%	643	107%
750	635	85%	698	93%
900	989	110%	736	82%
1300	1235	95%		
1500	1329	89%		
1800	1542	86%		

c. Traceability (controls, calibrators, or method):

The calibrators referenced in the package insert are sold separately and are in commercial distribution in the USA. They are distributed as Syva® Emit® Calibrator, levels 0-5. These calibrators were cleared by the FDA under Document Control No. k993755 on December 21, 1999.

d. Detection limit:

The sensitivity of the AMPH method is 125 ng/mL for the 1000 ng/mL cutoff (3µL sample size) and it represents the lowest concentration of AMPH that can be distinguished from zero. The sensitivity of the AMPH method is 95 ng/mL for the 300 and 500 ng/mL cutoffs (6 µL sample size). Sensitivity is defined as the concentration at two standard deviations above 0 ng/mL using Emit® Calibrator level 0 calibrator (n = 20).

e. Analytical specificity:

The tables below give the compounds this assay is designed to detect and the level at which the compounds have been found to give a response approximately equivalent to that of the selected cutoff (300, 500, or 1000 ng/mL d-methamphetamine).

Each concentration represents the reactivity level for the stated compound when it is added to a negative urine specimen. If a sample contains more than one compound detected by the assay, lower concentrations than those listed below may combine to produce a rate approximately equivalent to or greater than that of the cutoff calibrator.

Concentration of amphetamines producing a result approximately equivalent to the selected cutoff (300, 500, or 1000 ng/mL) d-methamphetamine cutoffs:

	Concentration (ng/mL) Giving a Response Approximately Equivalent to the Cutoff		
Compound	300 ng/mL cutoff	500 ng/mL cutoff	1000 ng/mL cutoff
d-Amphetamine *	329	529	1286
d, l-Amphetamine	528	1058	2139
d, l-Methamphetamine	491	818	1564
l-Amphetamine	2509	4996	10407
l-Methamphetamine	526	1049	2273
Methylenedioxyamphetamine (MDA)	1515	2410	3537
Methylenedioxymethamphetamine (MDMA)	3729	9594	20538
Methylenedioxyethamphetamine (MDEA)	3286	8359	18230

Concentration of amphetamines producing a result approximately equivalent to the selected cutoff (300, 500, or 1000 ng/mL) d-methamphetamine cutoffs:

	Concentration (ng/mL) Giving a Response Approximately Equivalent to the Cutoff		
Compound	300 ng/mL cutoff	500 ng/mL cutoff	1000 ng/mL cutoff
4-Chloramphetamine	2	5	10
Benzphetamine *	1	1	1
Bupropion	175	510	1038
Chloroquine	608	1687	3741
l-Ephedrine	355	1109	2242
Fenfluramine	17	45	105
Mephentermine	6	15	30
Methoxyphenamine	61	153	331
Nor-pseudoephedrine	40	93	188

Phenmetrazine	2	4	9
Phentermine	4	10	21
Phenylpropanolamine (PPA)	26	61	133
Propanolol	64	175	386
Pseudoephedrine	987	2834	5889
Quinacrine	1303	3776	8293
Tranylcypromine	28	59	126
Tyramine	98	232	503

*Benzphetamine metabolizes to amphetamine and methamphetamine.
Note: Selegiline, a prescription medication used in the treatment of Parkinson's disease, metabolizes to l-amphetamine and l-methamphetamine. Therefore, patients taking Selegiline may test positive by amphetamine assays.
Note: Specimens from patients taking chlorpromazine (Thorazine®) may produce positive results with this assay.

f. Assay cut-off:

Assay cutoffs are 300, 500 or 1000 ng/Ml. (See precision/ reproducibility studies above).

2. Comparison studies:
   a. Method comparison with predicate device:

Method comparison (cutoff = 300 ng/mL)

129 urine specimens were tested with the AMPH Flex® cartridge on the Dimension® system (cutoff = 300 ng/mL) and with the Syva® Emit® LL Plus Amphetamine Assay (9C309UL) on the Syva 30R® Biochemical System (cutoff = 300 ng/mL). All 129 specimens were also analyzed by GC/MS. Positives by GC/MS were determined by using criteria of amphetamine plus methamphetamine ≥300 ng/mL since there are no SAMSHA confirmation guidelines for the 300 cutoff. 24 of these specimens had total amphetamines by GC/MS within 25% of the 300 ng/mL cutoff. Results are summarized in the tables below:

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 300 ng/mL)		Syva 30R® Biochemical System (cutoff 300 ng/mL)	
		Positive	Negative
	Positive	70	2
	Negative	2	55

Discrepant s (ng/mL):

GC/MS Meth	*GC/MS Amph*	*GC/MS Total*	*Dimension AMPH*	*Syva 30R*
242	*61.1*	*303*	*315*	*273*
433	*< lod*	*433*	*325*	*298*
275	*70.2*	*345*	*278*	*300*
363	*< lod*	*363*	*204*	*301*

< lod: less than the limit of detection, < 25 ng/mL

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 300 ng/mL)		GC/MS (cutoff 300 ng/mL methamphetamine and amphetamine)	
		Positive	Negative
	Positive	72	0
	Negative	8	49

Discrepant s (ng/mL):

GC/MS	*GC/MS*	*GC/MS*	*Dimension*
253	*47.2*	*300*	*95*
311	*< lod*	*311*	*240*
326	*< lod*	*326*	*189*
313	*< lod*	*313*	*240*
363	*< lod*	*363*	*204*
255	*67.3*	*322*	*271*
275	*70.2*	*345*	*278*
279	*71*	*350*	*296*

< lod: less than the limit of detection, < 25 ng/mL

Method Comparison (cutoff = 500 ng/mL)

129 urine specimens were tested with the AMPH Flex® cartridge on the Dimension® system (cutoff = 500 ng/mL) and with the Syva® Emit® LL Plus Amphetamine Assay (9C309UL) on the Syva 30R® Biochemical System (cutoff = 500 ng/mL). All 129 specimens were also analyzed by GC/MS. Positives by GC/MS were determined by using the newly proposed SAMSHA guidelines by following the criteria of ≥ 250 ng/mL methamphetamine and ≥ 100 ng/mL amphetamine or ≥ 250 ng/mL amphetamine regardless of methamphetamine concentration. 28 of these had total amphetamines by GC/MS within 25% of the 500 ng/mL. Results are summarized in the tables below:

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 500 ng/mL)		Syva 30R® Biochemical System (cutoff 500 ng/mL)	
		Positive	Negative
	Positive	43	0
	Negative	1	85

Discrepant s (ng/mL):

GC/MS	*GC/MS*	*Dimension*	*Syva*
Meth	*Amph*	*AMPH*	*30R*
556	*62.7*	*405*	*598*

< lod: less than the limit of detection, < 25 ng/mL

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 500 ng/mL)		GC/MS (cutoff ≥250 ng/mL amphetamine or ≥ 250 ng/mL methamphetamine and ≥ 100 ng/mL amphetamine)	
		Positive	Negative
	Positive	34	9
	Negative	5	81

Discrepant s (ng/mL):

GC/MS	*GC/MS*	*Dimension*
Meth	*Amph*	*AMPH*
410	*36.7*	*550*
506	*43.6*	*572*
513	*44.8*	*564*
528	*47.9*	*572*
561	*48.6*	*507*
577	*50.5*	*574*
514	*56.1*	*534*
495	*58.4*	*548*
598	*64.5*	*561*
286	*169*	*366*
281	*173*	*388*
254	*174*	*344*
300	*179*	*398*
315	*186*	*393*

< lod: less than the limit of detection, < 25 ng/mL

Method Comparison (cutoff = 1000 ng/mL)

169 urine specimens were tested with the AMPH Flex® cartridge on the Dimension® system (cutoff = 1000 ng/mL) and with the Syva® Emit® LL Plus Amphetamine Assay (9C309UL) on the Syva 30R® Biochemical System (cutoff = 1000 ng/mL). Total amphetamine and methamphetamine values by GC/MS were reported for these 169 specimens. Positives by confirmation were determined according to the SAMSHA requirements by following the criteria of ≥ 500 ng/mL methamphetamine and ≥ 200 ng/mL amphetamines or ≥ 500 ng/mL amphetamines regardless of methamphetamine concentration.

Separate amphetamine and methamphetamine values were available for only 129 of these 169 specimens. Since separate amphetamine and methamphetamine values are required for confirmation testing according to SAMSHA guidelines, only those 129 samples were represented in the box plot shown in Table 10. Of these 129, there were 9 which had total amphetamines by GC/MS within 25% of the 1000 ng/mL cutoff. Results are summarized in the tables below:

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 1000 ng/mL)		Syva 30R® Biochemical System (cutoff 1000 ng/mL)	
		Positive	Negative
	Positive	62	0
	Negative	2	105

Discrepant s (ng/mL):

GC/MS Meth	*GC/MS Amph*	*Dimension AMPH*	*Syva 30R*
713	*534*	*929*	*1134*
494	*844*	*922*	*aar*

aar; above assay range, > 2000 ng/mL

AMPH Flex® Reagent Cartridge on the Dimension® clinical chemistry system (cutoff 1000 ng/mL)		GC/MS (cutoff ≥500 ng/mL amphetamine or ≥ 500 ng/mL methamphetamine and ≥ 200 ng/mL amphetamine)	
		Positive	Negative
	Positive	16	6
	Negative	8	99

Discrepant s (ng/mL):

GC/MS	*GC/MS*	*Dimension*
Meth	*Amph*	*AMPH*
1223	*118*	*1264*
1209	*127*	*1347*
1112	*172*	*1395*
1183	*174*	*1314*
1213	*177*	*1414*
1194	*180*	*1367*
631	*202*	*627*
652	*214*	*375*
713	*534*	*929*
496	*615*	*682*
390	*624*	*681*
333	*635*	*648*
494	*844*	*922*
161	*1032*	*770*

b. Matrix comparison:
Not applicable

3. Clinical studies:
   a. Clinical sensitivity:
   Not applicable

   b. Clinical specificity:
   Not applicable.

   c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:
   Analytical characterization of performance around the cut-off was demonstrated in the precision studies.

5. Expected values/Reference range:
   Not applicable.

N. Conclusion:

The submitted material in this premarket notification is complete and supports a substantial equivalence decision.